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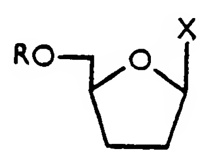

(I)

(57) Abstract

Compounds of formula (I) possess improved antiviral properties, especially in the treatment of neurological disorders caused by neurotropic viruses, for instance HIV infections. In the above formula R is an acyl group derived from a carboxylic acid or a carbonic acid, and X is a thymine or hypoxanthine group or an optionally N-acylated cytosine, ade-

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2',3' Dideoxyribofuranoxide derivatives.

This invention relates to antiviral compounds and more particularly to esters and amides of nucleoside derivatives which are active against human immunodeficiency virus (HIV), the retrovirus which causes the disease AIDS.

AIDS is a relatively new disease. It was discovered in 1981 and several thousand cases of the disease have been diagnosed since then. It is anticipated that the number will increase to at least several hundred thousand in the next few years. The situation is especially severe in several Central African countries. AIDS is fatal, and about 40% of all diagnosed cases have ended in death. Of those diagnosed as having AIDS three or more years ago it is estimated that 85% are now dead.

Clinical symptoms are weight loss, chronic diarrhoea, persisting fever and opportunistic infections due to loss of T-cells, thus upsetting the overall balance of the immune system. The patient loses his/her ability to combat otherwise insignificant infections.

Several different methods to combat the infection have been tried. Among the methods tried are stimulation of the immune system and conventional treatment of the (secondary) life-threatening infections. So far the most promising method has been to attack the replication of the HIV-virus. Several different compounds interfering with replication have been tried, e.g. phosphonoformate (Foscarnet), suramin, Evans Blue, 3'-azido-3'-deoxythymidine (AZT) and 2', 3'-dideoxynucleosides.

European Patent Application No. 0196185A, for instance, describes pharmaceutical compositions

containing AZT, a known compound which has shown great promise in the treatment of AIDS and AIDS-related complex. It is believed that AZT works by inhibiting reverse transcriptase, a vital enzyme in the life cycle of retroviruses.

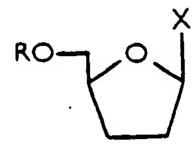
Further work has been done on alternative reverse transcriptase inhibitors which might avoid the limitations and drawbacks of AZT, for instance bone marrow suppression or the need for frequent administration of relatively large quantities, and among those suggested have been the 2',3'-dideoxy-nucleosides.

The synthesis and activity of these compounds have been described (Mitsuya and Broder, Proc. Natl. Acad. Sci. 83, 1911 (1986)) and it was demonstrated that both the 2' and 3' positions must be unsubstituted while the 5'-hydroxy group must be present, presumably to allow *in vivo* conversion to the corresponding nucleotides. The compounds seem to have lower toxicity and higher potency than AZT; 2',3'-dideoxycytidine is now undergoing clinical trials.

European Patent Application No 0206497A discloses 2',3'-dideoxyribofuranoside derivatives of cytosine or purine bases as antiviral compounds. While there is reference to esters of these compounds as possible metabolic precursors, there is no suggestion that esters would possess any advantageous properties compared with the parent 5'-hydroxy compounds and no esters are specifically named or their synthesis exemplified. There is no reference to any corresponding thymidine compounds or of any nucleoside derivatives having N-acylated amino groups.

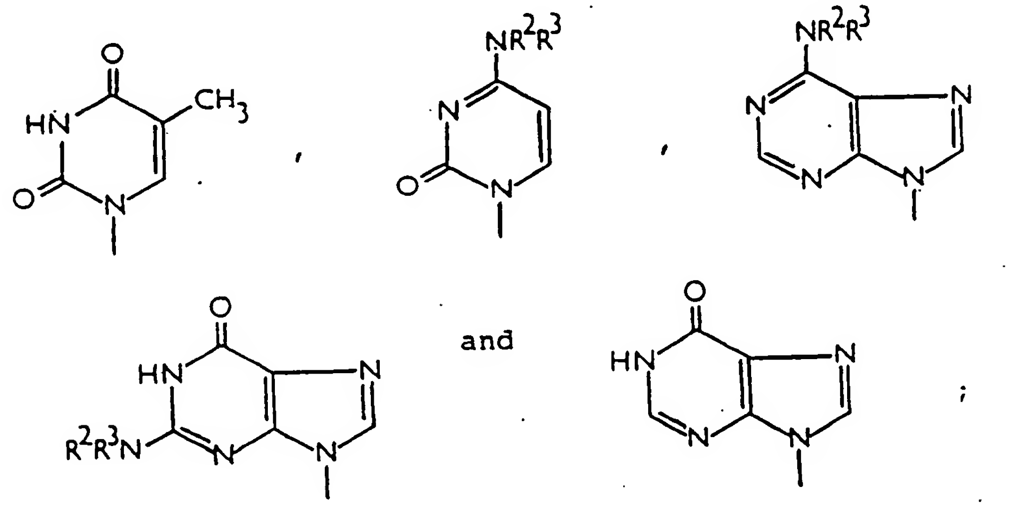
We have now found that esterification of the 5'-hydroxy group and/or amidation of amino groups present in the purine or pyrimidine ring can give significant advantages in terms of uptake, overall activity and site of action.

Thus according to one feature of the invention we provide pharmaceutical compositions comprising as active ingredient one or more compounds of formula (I)



(I)

wherein R is a hydrogen atom or a physiologically acceptable acyl group of formula R^1.CO- or R^1.O.CO-, R^1 being an optionally substituted alkyl or aryl group, and X is selected from



wherein R^2 and R^3, which may be the same of different, each represent a hydrogen atom or a physiologically acceptable acyl group of formula R^4.CO- or R^4.O.CO-, R^4 being an optionally substituted alkyl or aryl group, with the proviso that at least one of R and R^2 must be an acyl group, and/or salts thereof. X is advantageously a substituted or unsubstituted thymine group.

According to a further feature of this invention we provide for the use of compounds of formula (I) as hereinbefore defined, and/or salts thereof, in the manufacture of a medicament for the treatment of retrovirus infections, in particular neurotropic viruses and especially HIV infections.

The compositions may be formulated in conventional manner by admixture of one or more compounds of formula (I) as defined above with excipients and/or carriers.

The acyl groups R, R^2 and R^3 in formula (I) are preferably C_{1-20} acyl groups and more preferably C_{2-18} acyl groups (the term "acyl" as used herein is intended to include groups derived from either carboxylic or carbonic acids). The acyl group may be saturated, unsaturated or contain an aromatic system, and can include, for instance, C_{1-8} alkanoyl and alkenoyl groups and C_{7-20} aroyl groups. The acyl groups may be substituted, for instance by hydroxy or carboxy groups. Alkanoyl groups can carry C_{6-12} aryl groups. Suitable examples include formyl, acetyl, butyryl, pivaloyl, hexanoyl, stearoyl, palmitoyl, succinoyl, phenylacetyl, benzoyl, isobutyloxycarbonyl, ethyloxycarbonyl and benzyloxycarbonyl groups.

The compositions wherein R^2 and R^3 are hydrogen and R is a group R^1.O.CO- as defined above form one particularly prefered aspect of the invention. Another prefered group of compounds according to the invention are those in which R^2 is an acyl group as defined above, R^3 is hydrogen or an acyl group as defined above and R is hydrogen or an acyl group as defined above. In general R^3 is preferably hydrogen.

The salts of the compounds of formula (I) may be acid addition salts with organic or inorganic acids, for instance hydrochloric or phosphoric acid or methanesulphonic acid, ethane disulphonic acid, 2-naphthylsulphonic acid, pivalic acid and

pamoic acid. Antiviral counter-ions such as phosphonoformate or suramin may also be used. Organic or inorganic base salts may be formed with acidic groups present in the molecule; suitable counter-ions include alkali metal ions such as sodium and potassium ions, divalent ions such as calcium and zinc ions and organic ions such as tetraalkylammonium and choline or ions derived from meglumine or ethylenediamine. Salts according to the invention may be formed by reaction of the compound of formula (I) with an appropriate acid or base.

The compositions according to the invention may be used in the treatment and/or prophylaxis of retrovirus infections, in particular HIV infections, and such a method forms a further feature of the invention.

It is believed that the esters of formula (I) are not themselves inhibitors of reverse transcriptase but are converted *in vivo* to the 5-hydroxy-2,3-dideoxynucleosides. Nevertheless the esterification and/or amidation of the hydroxy and amino groups gives surprising advantages in terms of uptake and sustained activity. The compounds of formula (I) are more lipophilic than the parent compounds and this permits rapid and efficient absorption from the gastro-intestinal tract; the absorption rate may be optimised by careful choice of the acyl group to give the desired balance of lipophilicity and hydrophilicity. The lipophilic nature of the compunds of formula (I) also gives the molecules the ability to penetrate the cell membranes more easily and leads to higher intracellular concentrations, giving an improved dose/effect ratio. The steady hydrolysis of the ester compounds ensures a sustained concentration of the active compound in the cell and thereby permits longer intervals between doses, overcoming a significant drawback of the prior art compounds such as AZT.

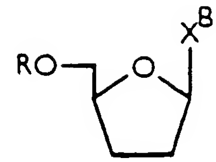
Finally, the compounds according to the invention can penetrate the blood-brain barrier and thus permit treatment of the neurological disorders which have been observed to be related to the presence of neurotropic viruses, e.g. retroviruses such as HIV, and lentiviruses (Yarchoan et al, The Lancet, January 17, 1987, page 132). This is a significant advantage compared to the corresponding unsubstituted compounds or other antiviral compounds and is not referred to anywhere in the prior art, for instance in EP-A-0206497. Attempts have been made to treat these neurological disorders with AZT but with limited success.

The invention thus further provides a method of treatment of neurological disorders caused by neurotropic viruses wherein an effective dose of a compound of formula (I) or a salt thereof is administered to a patient suffering from such a disorder.

Many of the compounds of formula (I) are new and form a still further feature of the invention. Thus we also provide compounds of formula (I) wherein R and X are as hereinbefore defined, with the further proviso that when R is an acetyl group then X is not a thymine radical; when R is a benzoyl group then X is not a thymine radical or an N-unsubstituted cytosine radical (i.e. a cytosine group X wherein R^2 is a hydrogen atom); and when R is a 3-(trifluoromethyl)-benzoyl group then X is not an N-unsubstituted adenine radical (i.e. an adenine group X wherein R^2 is a hydrogen atom); and salts thereof.

The known compounds of formula (I) are described in a number of publications; there is, however, no indication that they might be active against the HIV virus or have any other medical use.

Compounds of formula (I) and, in particular, the novel compounds defined above, may be prepared by acylation of compounds of formula (II)



(II)

[wherein R is as hereinbefore defined and X^B is as hereinbefore defined for X except that R and R^2 and/or R^3 may each additionaly represent a protecting group, with the proviso that at least one of R, R^2 and R^3 is a hydrogen atom] with an acylating agent serving to introduce an acyl group R^1CO-, R^1OCO-, R^4CO- or R^4OCO-, followed where required by removal of any protecting groups and/or unwanted acyl substituents.

It should be noted that where, in the starting material, more than one of R, R^2 and R^3 is hydrogen, diacylation or triacylation may occur.

In general, we have found that using acid anhydrides as acylating agents to introduce a group R^1CO or R^4CO O-acylation takes place more readily than N-acylation whereas using acid halides, N-acylation or even N-diacylation predominates. However, N-acyl groups R^4CO- may be removed selectively, for example by reaction with a phenol such as p-methylphenol. Where it is desired to ensure that O-acylation to introduce a group R^1OCO- is effected while R^2 and R^3 remain as hydrogen atoms, it may be desirable to protect the exocyclic nitrogen atom first, to form a compound of formula (I) in which R^2 and R^3 are N-protecting groups, these being removed after introduction of the O-acyl group. Such protecting groups may, in fact, be conventional N-protecting groups including other groups R^4OCO- which may be selectively removed in the presence of the O-acyl group R^1OCO-. Thus, for example, an N-benzyloxycarbonyl group may be used to protect an exocylic

amino and if the O-acyl group R^4OCO- is not one which is removable by reduction, for example a straight chain alkoxycarbonyl group, the N-benzyloxycarbonyl group can readily be removed selectively using hydrogen and a noble metal catalyst such as palladium.

In general, where more than one of R, R^2 and R^3 are hydrogen, a mixture of acylated compounds may be produced. However, the individual components may readily be separated, for example by chromatography.

Suitable acylating agents for use in the reaction have the formula Ac-L where L is a leaving group. When the acyl group Ac- is derived from a carboxylic acid, i.e. is of formula R^1-CO- or R^4-CO-, then suitable acylating agents include the acid halides and acid anhydrides advantageously in the presence of a base; when the acyl group is derived from a carbonic acid, i.e. is of formula R^1.O.CO- or R^4.O.CO-, then acylating agents include the haloformate esters and reactive carbonic acid diesters. The base for use in the reaction with the acid halide or anhydride may, for example, be a heterocyclic base such as pyridine or dimethylaminopyridine. The latter increases the speed of the reaction and may be used advantageously with pyridine. The reaction will normally be carried out in the presence of an inert solvent such as dimethyl-formamide or a halogenated hydrocarbon such as dichloromethane.

The starting compounds of formula (II) wherein R, R^2 and R^3 are all hydrogen atoms are well described in the literature - see, for instance, Lin et al, J. Med. Chem. 30, 440 (1987).

The pharmaceutical compositions according to the invention may be formulated conventionally by means well known in the art, and may be administered by any convenient route, for instance orally, rectally, vaginally, intraveneously or intramuscularly. Examples of suitable formulations include tablets

and capsules, aqueous formulations for intravenous injection and oil-based formulations for intramuscular injection. Suitable dosages will lie in the range 0.1 to 100mg per kilogram of bodyweight per 24 hour period. The compositions according to the invention may also contain other active antivirals for instance acyclovir, phosphonoformate, suramin, Evans Blue, interferons or AZT.

The invention is illustrated by the following Examples. Capsugel is a Trade Mark.

Example 1

2',3'-Dideoxy-5'-O-palmitoyl-cytidine

Palmitoyl chloride (2.80g, 10.2 mmol) is added dropwise during 30 minutes to a stirred solution of 2',3'-dideoxycytidine (2.11g, 10 mmol) in dry 1:1 pyridine/N,N-dimethylformamide (130ml) at 0°C. The mixture is stirred for 30 hours. Water (20ml) is added and the mixture is evaporated. The product is purified on a column of silica gel with methanol/-chloroform/hexane as solvent.

Example 2

5'-O-Butyryl-2',3'-dideoxy-adenosine

Butyryl chloride (1.09g, 10.2mmol) is added dropwise during 30 minutes to a stirred solution of 2',3'-dideoxyadenosine (2.45g, 10 mmol) in dry 1:1 pyridine/N,N dimethylformamide (100ml) at 0°C. The mixture is stirred at 0°C for 30 hours, water (20ml) is added and the mixture is evaporated. The product is purified on a column of silica gel with methanol/-chloroform as solvent.

Example 3

2',3'-Dideoxy-5'-O-hexanoyl-thymidine

2',3'-Dideoxythymidine (0.0100 g, 4.4203×10^{-5} mole) was dissolved in a mixture of pyridine (0.44ml) and dimethylformamide (0.44 ml) (both distilled from calcium hydride) and cooled to 0°C. Hexanoyl chloride (freshly distilled, 0.00682 ml, 4.8622×10^{-5} mole) was added with a syringe. The mixture was stirred for 48 hours under nitrogen at 0°C, when thin layer chromatography showed partial conversion. N,N-Dimethyl-4-aminopyridine (0.0001 g) was added under exclusion of air and the mixture was stirred

for a further 24 hours when hexanoyl chloride (0.00682 ml, 4.8622 x 10^{-5}mole) was added. After a further 24 hours water (2 ml) was added and the solution was evaporated under high vacuum. Water was added four times (4 x 2 ml) with high vacuum evaporation between each addition. The resulting semi-solid was dissolved in chloroform and applied to a silica column (E. Merck 9385) and eluted with chloroform and chloroform: ethanol 99:1. The title compound eluted first. Yield 0.0085 g (59.3%), mp 94-96 °C (uncorrected).

^{1}H NMR($CDCl_3$ 300 MHz) δ : 0.90 (t, 3H, $\underline{J}$ 6.8 Hz), 1.32(m, 4H), 1.66(m,2H), 1.83(m,1H), 1.95 (s,3H), 2.05(m, 2H), 2.37(t, 2H, $\underline{J}$ 7.5 Hz), 2.45(m, 1H), 4.33(m, 3H), 6.08(d d, 1H, $\underline{J}_1$ 4.4 Hz, $\underline{J}_2$ 6.70 Hz), 7.40(s, 1H), 8.54(bs, 1H).

^{13}C NMR ($CDCl_3$ 75 MHz) δ : 12.674, 13.879, 22.288, 24.593, 25.919, 31.285, 32.223, 34.183, 64.801, 78.462, 86.180, 110.508, 135.272, 150.163, 163.530, 173.442.

Example 4

2',3'-Dideoxy-5'-0'-palmitoyl-thymidine

2',3'-Dideoxythymidine (0.0100 g 4.4203 x 10^{-5}mole) was dissolved in a mixture of pyridine (0.221 ml) and dimethylformamide (0.221 ml) (both distilled from calcium hydride) and cooled to 0°C. Palmitoyl chloride (freshly distilled, 0.01476 ml, 4.8623 x 10^{-5}mol) was added with a syringe. The mixture was stirred for 4 days under nitrogen, when thin layer chromatography showed partial conversion. Pyridine (0.221 ml) and dimethylformamide (0.221 ml) (both cooled to 0°C) were added and the resulting mixture stirred at 10°C for 24 hours, when water (2ml) was added. The resulting mixture was evaporated at low temperature under high vacuum. Water was added four more times (4 x 2 ml), with high vacuum

evaporation between each addition. The resulting semisolid was suspended in chloroform and applied to a silica column (E. Merck 9385) and eluted first with chloroform, then with chloroform:methanol 9:1. The title compound eluted first. Yield 0.0076g (34.7%) mp 92-94 °C (uncorrected.). ^{1}H NMR($CDCl_3$ 300 MHz) δ : 0.88(t 3H, J 7.1 Hz), 1.25(m+s 20H), 1.61(m 2H), 1.83(m 1H), 1.95(s 3H), 2.04(m 2H), 2.37(t 2H,J 3 Hz), 2.42(m 1H), 4.32(m 3H), 6.07(dd 1H), 7.40(s 1H), 8.20(broad s, 1H). ^{13}C NMR($CDCl_3$ 75 MHz) δ: 12.68, 14.12, 22.69, 24.91, 25.89, 29.15, 29.25, 29.36, 24.46, 29.60, 29.68(large peak - 5 carbon atoms), 31.93, 32.23, 78.47, 86.16, 110.48, 135.25, 150.03, 163.35, 173.48.

Example 5

$\underline{N}^4$,5'-$\underline{O}$-Dibenzoyl-2',3'-dideoxy-cytidine and $\underline{N}^4$-benzoyl-2',3'-dideoxy-cytidine

2',3'-Dideoxy cytidine (0.0200 g, 9.469x10^{-5} mole) and N,N-dimethylaminopyridine (0.0127g, 10.367x10^{-5} mole) were dissolved in dichloromethane (1.0 ml, distilled from calcium hydride). Benzoyl chloride (0.0146g, 10.367x10^{-5} mole) was added with a syringe. The resulting mixture was stirred for 24 hours before distilled water (2.0 ml) was added. After complete evaporation (high vacuum) the residue was chromatographed on a silica column with chloroform and chloroform:ethanol 9:1. $\underline{N}^4$,5'-0-Dibenzoyl-2',3'-dideoxy-cytidine eluted first, followed by $\underline{N}^4$-benzoyl-2',3'-dideoxy-cytidine.

$\underline{N}^4$,5'-$\underline{O}$-Dibenzoyl-2',3'-dideoxy-cytidine

Yield 0.0144 g (36.4%) M.p. 180-190°C (uncorrected)(not

recrystallized). ^{1}HNMR($CDCl_3$, 300 MHz) δ : 1.76-1.92 (m, 1H), 2.04-2.16 (m, 1H), 2.18-2.30(m, 1H), 2.54-2.70(m, 1H), 4.47-4.56(m, 1H, H4'), 4.56 (broad d, 2H, H5'), 6.10(dd, 1H,H1'), 7.43(d, 1H,H5), 7.46-7.54(broad t, 4H,Ph), 7.56-7.64 (broad t, 2H, Ph), 7.86 (broad d, 2H,Ph), 8.05 (broad d, 2H,Ph), 8.26 (d, 1H, H6, _J_ 7.46 Hz), 8.59 (broad, 1H, NH). ^{13}C NMR($CDCl_3$, 75 MHz) δ : 25.03, 33.42, 64.73, 80.16, 88.27, 95.90, 127.42, 128.69, 129.06, 129.36, 129.57, 133.16, 133.16, 133.64, 144.19, 162.06, 166.27.

_N_^{4}-benzoyl-2',3'-dideoxy-cytidine

Yield 0.0060 g (28.0%) M.p. 202-205°C (uncorrected) (not recrystallized). ^{1}HNMR($CDCl_3$, 300 MHz) δ : 1.85-2.05(m, 2H), 2.16-2.30(m, 1H), 3.78-3.88 and 4.06-4.16(ABX, 2H, H5'), 4.29(m, 1H, H4'), 6.12(dd, 1H,H1'), 7.41-7.64(m, 3H,Ph), 7.92 (broad d, 2H, Ph), 8.51(d, H6), 8.52 (broad, 1H, NH).

^{1}NMR($DMSOd_6$; 300 MHz) δ : 1.72-1.90 (m, 2H), 1.90-2.10(m, 1H), 2.35-2.48(m, 1H), 3.55-3.65 and 3.72-3.82 (2H, ABX, H5'), 4.12 (m, 1H, H4'), 5.16(t, 1H, OH), 5.95(dd, 1H, H1'), 7.33(d, 1H, H5), 7.47-7.56(broad t, 2H, Ph), 7.59-7.66 (broad t, 2H, Ph), 7.59-7.66(broad t, 1H, Ph), 7.99(broad d, 2H, Ph), 8.55(d, 1H, H6 _J_ 7.38 Hz), 11.22(s, 1H, NH). ^{13}C NMR($CDCl_3$ + 5% $DMSOd_6$, 75 MHz) δ : 23.66, 33.37, 62.00, 82.96, 87.82, 95.76, 127.53, 128.53, 132.34, 132.66, 132.95, 145.30, 154.91, 162.19.

Example 6

5'-_O_-benzoyl-2',3'-dideoxy-cytidine

_N_^{4},5'-_O_-Dibenzoyl-2',3'-dideoxy-cytidine (0.0142g, 3.385×10^{-5} mole) and p-methylphenol (0.0183 g,

1.689×10^{-4} mole) were dissolved in toluene (0.5ml distilled from sodium and benzophenone) and stirred at room temperature for 24 hours. The temperature was then increased to 120°C and the mixture was stirred for a further 12 hours. At this time thin layer chromatography (silica, chloroform:ethanol 99:1 and 9:1) revealed almost complete consumption of the starting material. The toluene was evaporated and the residue chromatographed on silica with chloroform, chloroform:ethanol 99:1 and chloroform:ethanol 9:1. The compounds were eluted in the following order: p-methylphenol, $\underline{N}^4$,5'-$\underline{O}$-dibenzoyl-2',3'-dideoxy-cytidine and 5'-$\underline{O}$-benzoyl-2',3'-dideoxy-cytidine. Recovered $\underline{N}^4$,5'-$\underline{O}$-dibenzoyl-2',3'-dideoxy-cytidine 0.0018 g (13 %).

Yield (5'-$\underline{O}$-benzoyl-2',3'-dideoxy-cytidine) 0.0092g (86.0%). Glassy material. M.p. 114-116°C (uncorrected). (not recrystallized) ^{1}HNMR($CDCl_3$, 300 MHz) δ : 1.67-1.86 (m, 1H), 2.02-2.21(m,2H),2.44-2.62(m,1H),4.41-4.46 (m,1H,H4'), 4.52-4.68 (ABX,2H,H5'), 5.54(d, H5, $\underline{J}$ 7.2 Hz), 6.08(dd, H1'), 7.44-7.50(broad t, 2H Ph), 7.57-7.64(broad d, 1H, Ph), 7.81(d, H6, $\underline{J}$ 7.2 Hz), 8.04(broad d 2H, Ph), 5.1-6.3(very broad, 2H, NH_2). ^{13}C NMR($CDCl_3$, 75 MHz) δ : 25.51, 33.28, 65.28, 73.98, 79.25, 87.64, 93.07, 128.55, 129.57, 129.63, 133.41, 140.93, 155.77, 164.46.

Example 7

$\underline{N}^4$-Benzoyl-2',3'-dideoxy-5'-$\underline{O}$-palmitoyl-cytidine

$\underline{N}^4$-Benzoyl-2',3'-dideoxycytidine (0.0215 g, 6.797×10^{-5} mole) was dissolved in a mixture of pyridine (0.25 ml) and dimethylformamide (0.25 ml). N,N-dimethylaminopyridine (0.0083 g, 6.797×10^{-5} mole) and palmitoyl chloride (0.0374 g, 1.359×10^{-4} mole) were added at room temperature. The resulting

mixture was heated to 60°C and stirred at this temperature for 12 hours, when a new aliquot of palmitoyl chloride (0.0374 g, 1.359×10^{-4} mol) was added at room temperature. The resulting mixture was heated to 60°C and stirred at this temperature for 12 hours, when a new aliquot of palmitoyl chloride (0.0374g, 1.359×10^{-4}mol) and pyridine (0.25 ml) were added at room temperature. The temperature was again raised to 60°C and kept there for a further 8 hours. Water (2 ml) was added and the solvents removed at high vacuum. The resulting semi-solid was applied to a silica column and eluted with chloroform and chloroform:ethanol 99:1. The product was isolated as a white powder contaminated with palmitic acid. No attempt was made to remove the palmitic acid at this stage. Yield (after subtracting excess palmitic acid from the ^{1}HNMR-integration): 0.0199 g (52.8 %).

^{1}HNMR($CDCl_3$, 300 MHz) δ : 1.95(t, CH_3), 1.2-1.6 (m, CH_2-alkyl), 2.06-2.20(m, 1H), 2.25-2.35(m, 1H), 2.35-2.50(m,4H), 2.60-2.75 (m,1H), 4.40-4.58(m, 3H, H4' and H5'), 6.15(dd, H1'), 7.55-7.80(m, 4H, Ph+H5), 8.05 (broad d, 2H, Ph), 8.26(d, 1H,H6).

^{13}C NMR($CDCl_3$, 75 MHz) (sample containing free palmitic acid) δ : 14.12, 22.69, 24.71, 24.95, 29.09, 29.17, 29.27, 29.36, 29.36, 29.45, 29.48, 29.60, 29.68, (broad-large resonance-several carbon atoms), 31.92, 33.29, 34.06, 34.22, 64.22, 80.13, 88.43, 96.07, 128.15, 128.76, 132.86, 133.13, 144.80, 163.01, 173.43, 179.60.

<u>Example 8</u>

2',3'-Dideoxy-5'-<u>O</u>-palmitoyl-cytidine

<u>N</u>^{4}-benzoyl-2',3'-dideoxy-5'-<u>O</u>-palmitoyl-cytidine (0.0199 g, 3.587×10^{-5} mole) (contaminated by some palmitic acid) and p-methylphenol (0.0256 g, 2.367×10^{-4}

mole) were dissolved in toluene (0.5 ml, distilled from sodium and benzophenone). The resulting solution was refluxed for 15 hours. The toluene was evaporated and the residue chromatographed on a silica column and eluted with chloroform, chloroform:ethanol 99:1 and chloroform:ethanol 9:1. The benzoate of the p-methylphenol and the palmitic acid contamination from the preceding step were eluted first followed by p-methylphenol, $\underline{N}^4$-benzoyl-2',3'-dideoxy-5'-$\underline{O}$-palmitoyl-cytidine and 2',3'-dideoxy-5'-$\underline{O}$-palmitoyl-cytidine. Yield (2',3'-dideoxy-5'-$\underline{O}$-palmitoyl-cytidine)0.0107 g (66.2 %) M.p. 120-122 °C (uncorrected) (not recrystallized).

^{1}HNMR($CDCl_3$, 300 MHz) δ : 0.88 (t, CH_3), 1.2-1.38 (broad s, 22H, alkyl chain), 1.57-1.76(m, 4H), 1.96-2.06(m, 1H), 2.06-2.18(m, 1H), 2.35(t, CH_2-COO), 2.43-2.58(m, 1H), 4.32-4.40(m, 3H, H5'+H4'), 5.0-6.0 (very broad 2H, NH_2), 5.67 (d, 1H, H5, $\underline{J}$ 7.51 Hz), 6.05(dd, H1'), 7.79(d, H6, $\underline{J}$ 7.51 Hz).

^{13}C NMR($CDCl_3$, 75 MHz) δ : 14.13, 22.69, 24.91, 25.50, 29.16, 29.27, 29.36, 29.47, 29.61, 29.65 and 29.69 (these two resonances represent several carbon atoms) 31.92, 33.16, 34.21, 64.81, 73.99, 79.18, 87.71, 92.82, 96.89, 141.09, 155.74, 165.40, 173.49.

Example 9

2',3'-dideoxy-5'-$\underline{O}$-isobutyloxycarbonyl-thymidine

2',3'-Dideoxythymidine (0.0100 g, $4.42.10^{-5}$ mole) and N,N-dimethylaminopyridine (0.0059 g, $4.8x10^{-4}$ mole) were suspended in dry dichloromethane (1ml) and cooled to 0°C. Isobutyl chloroformate (12.62 ul, $8.84x10^{-5}$ mole) was added. The resulting mixture was stirred at room temperature for 11 days. Water (2 ml) was added. After complete evaporation at

high vacuum, the residue was chromatographed on a silica column. The product was eluted with chloroform and chloroform:ethanol = 99:1

Yield 0.0119 g (82.4%), mp 128-130 °C (uncorrected) (not recrystallised).
^{1}HNMR ($CDCl_3$; 300 MHz) δ : 0.96(d, 6H, J 6.75 Hz), 1.95(s, 3H), 1.91-2.18(m, 4H), 2.4(m, 1H), 3.97(d, 2H, J 6.59 Hz), 4.32(m, 1H), 4.40(ABX, 2H), 6.12(q, 1H), 7.56(s, 1H), 8.47(broad s, 1H).
^{13}CNMR($CDCl_3$, 75 MHz) δ : 12.51, 18.89, (2 carbon atoms), 25.40, 27.81, 32.46, 67.73, 74.61, 78.41, 85.97, 110.58, 135.64, 150.22, 155.21, 163.60.
MSCI (isobutane): 327(M+1, 41.4), 209(5.3), 202(7.4), 200(67.0), 169(16.5), 167(18.1), 145(58.4), 127(100), 83(24.6).

Example 10

N^4,5'-O-Di(benzyloxycarbonyl)-2',3'-dideoxy-cytidine and N^4-Benzyloxycarbonyl-2',3'-dideoxy-cytidine

2',3'-Dideoxy-cytidine (0.0250 g, 1.178 x 10^{-4} mole) was dissolved in a mixture of pyridine (0.25 ml) and N,N-dimethylformamide (0.25 ml) and cooled to 0 °C. Benzyl chloroformate (0.0603 g, 3.534 x 10^{-4} mole) was added with a syringe. N,N-dimethylaminopyridine (0.0144 g, 1.178 x 10^{-4} mole) was added and the resulting solution stirred at room temperature for 12 hours. Thin layer chromatography (silica, chloroform:ethanol 9:1) indicated partial conversion at this point. The mixture was cooled to 0°C and benzyl chloroformate (0.0603 g, 3.534 x 10^{-4} mole) was added with a syringe. The mixture was stirred for a further 24 hours at room temperature. Water (2 ml) was then added and the solution was evaporated at high vacuum. The resulting semi-solid was applied to a silica column and eluted with chloroform and chloroform: ethanol 99:1.

$\underline{N}^4$-Benzyloxycarbonyl-2',3'-dideoxy-cytidine

Yield 0.0385 g (84.9 %). Glassy material. ^{1}HNMR ($CDCl_3$, 300 MHz) δ : 1.82-1.98 (m, 2H), 2.10-2.22 (m, 1H), 2.42-2.59 (m, 1H), 3.05 (broad, 1H, OH), 3.76 and 3.80 (ABX, 2H, H5'), 4.24 (m, H4'), 5.17 (s, 2H, O-$\underline{CH}_2$-Ph), 6.06 (dd, 1H,H1'), 7.24 (d, 1H, H5, $\underline{J}$ 7.57 Hz) 7.93 (broad, 1H, NH), 8.50 (d, 1H, H, $\underline{J}$ 7.57 Hz) ^{13}CNMR ($CDCl_3$, 75 MHz) δ : 24.10, 33.37, 62.93, 67.85, 82.72, 88.19, 94.26, 128.33, 128.44, 128.64, 134.94, 145.01, 152.28, 155.23, 162.11.

$\underline{N}^4$,5'-$\underline{O}$-di(benzyloxycarbonyl)-2',3'-dideoxy-cytidine was also isolated in small quantities. This product coeluted with several contaminants and decomposition products. The product was finally isolated by careful rechromatography on a silica column with pure chloroform as eluent.

$\underline{N}^4$,5'-$\underline{O}$-di(benzyloxycarbonyl)-2',3'-dideoxy-cytidine.

Yield: 0.0075 g (13.2%). Glassy material. ^{1}HNMR($CDCl_3$, 300MHz) δ : 1.64 - 1.82 (m, 1H), 1.92-2.08 (m, 1H), 2.08-2.22 (m, 1H), 2.46-2.62 (m, 1H), 4.32-4.40 (m, 1H, H5'), 4.34-4.52 (ABX, 2H, H4'), 5.21 (s, 2H, $\underline{CH}_2$-O), 5.23 (s, 2H, $\underline{CH}_2$-O), 6.06 (dd, 1H,H1'), 7.21 (d, H5, $\underline{J}$ 7.38 Hz), 7.39 (broad, 10H, 2Ph), 7.5 (broad, 1H, NH), 8.16 (d, 1H, H6, $\underline{J}$ 7.38 Hz). ^{13}C NMR($CDCl_3$, 75 MHz) δ : 24.83, 33.23, 67.67, 67.95, 70.06, 79.51, 88.10, 94.16, 128.36, 128.52, 128.71, 134.86, 144.05, 152.12, 154.93, 162.05.

Example 11

5'-O-Acetyl-2',3'-dideoxy-cytidine and N^4,5'-O-diacetyl-2',3'-dideoxy-cytidine.

2',3'-dideoxy-cytidine (0.0300 g, 1.42×10^{-4} mole) and N,N-dimethylaminopyridine (0.0087 g, 7.10×10^{-5} mole) were dissolved in a mixture of dichloromethane (1 ml) and pyridine (1 ml). The resulting solution was cooled to 0°C and acetic anhydride (0.0290 g, 2.84×10^{-4} mole) was added with a syringe. The reaction mixture was stirred at room temperature for 24 hours. Water (4 ml) was then added and the solvents were removed by high vacuum evaporation. The resulting solid was chromatographed on a silica column and eluted with chloroform:ethanol 99:1, chloroform:ethanol 9:1 and chloroform:ethanol 7:3.

5'-O-acetyl-2',3'-dideoxy-cytidine

Yield 0.0120 g (31.3 %) Oil, glassy material ^{1}HNMR($CDCl_3$, 300 MHz)δ : 1.60-1.78(m, 1H), 1.94-2.20(m, 2H), 2.12(s, 3H), 2.40-2.58(m, 1H), 4.32(m, 3H, H4'+H5'), 5.77(d, 1H, H5, *J* 7.20 Hz), 6.05(dd, 1H, H1'), 7.40(d, 1H, H6, *J* 7.20 Hz), 5.0-7.3(very broad, 2H, NH_2).
^{13}CNMR ($CDCl_3$, 75 MHz, pulse delay 3s)δ : 20.85, 25.54, 33.02, 65.04, 78.98, 87.54, 93.58, 140.61, 155.76, 165.63, 170.63.

N^4,5'-O-diacetyl-2',3'-dideoxy-cytidine

Yield 0.0268 g (63.9%) M.p. 230°C (uncorrected) (not recrystallized).
^{1}HNMR ($CDCl_3$, 300 MHz)δ : 1.63-1.80(m, 1H), 1.96-2.09(m, 1H), 2.10-2.23(m, 1H), 2.15(s, 3H), 2.30(s, 3H), 2.48(m, 1H), 4.30-4.45(m, 3H), 6.06(dd, 1H, H1'), 7.46(d, 1H, H5 *J* 7.54 Hz), 8.19(d, 1H, H6, *J* 7.54 Hz), NH not seen. ^{13}CNMR ($CDCl_3$, 75 MHz,

pulse delay 3s) δ : 20.84, 24.85, 33.21, 64.40, 79.91, 88.20, 96.03, 143.96, 155.04, 162.90, 170.49, 171.12.

Example 12

$\underline{N}^6$,5'-$\underline{O}$-Dibenzoyl-2',3'-dideoxy-adenosine and 2',3'-dideoxy-$\underline{N}^6$,$\underline{N}^6$,5'-$\underline{O}$-tribenzoyl-adenosine

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2',3'-Dideoxyadenosine (0.0250 g, 1.063×10^{-4} mole) was dissolved in a mixture of dichloromethane (1.0 ml) and pyridine (0.25 ml) and cooled to 0°C. Benzoyl chloride (0.0299 g, 2.125×10^{-4} mole) was added with a syringe and the temperature raised to room temperature. The mixture was stirred for 24 hours, recooled to 0°C and benzoyl chloride (0.0299 g, 2.125×10^{-4} mole) was added for the second time. The reaction mixture was stirred for a further 12 hours at room temperature. Water (4ml) was added and solvents and water were removed by high vacuum evaporation. The resulting semi-solid was chromatographed on a silica column and eluted with chloroform and chloroform:ethanol 99:1. Not all fractions contained pure compounds after the first column. The impure fractions were chromatographed a second time on a silica column and eluted with chloroform and chloroform: ethanol 99:1.

$\underline{N}^6$,5'-$\underline{O}$-Dibenzoyl-2',3'-dideoxy-adenosine

Yield: 0.0387 g (82%). Colorless oil. ^{1}HNMR($CDCl_3$, 300 MHz) δ : 2.17-2.37(m, 2H), 2.57-2.71(m,1H), 2.73(m, 1H), 4.48-4.68(ABX+m, 3H, H5'+H4'), 6.37(dd, 1H, H1') 7.39-7.66(complex pattern, 6H, 2Ph), 7.87-8.06 (complex pattern 4H, 2Ph), 8.26(s,1H), 8.79(s,1H), 8.99(broad s, 1H, NH). ^{13}C NMR($CDCl_3$, 75 MHz, pulse delay 3s) δ : 26.39, 32.34, 65.51, 79.57, 86.23, 127.79, 128.48, 128.88, 129.49, 129.59, 132.77, 133.68, 141.38, 149.40, 151.05, 152.58, 164.46, 166.30.

2',3'-Dideoxy-N^6,N^6,5'-O-tribenzoyl-adenosine

Yield: 0.0087 g (15%) Clear glassy material. ^{1}HNMR(CDCl$_3$ 300 MHz)δ: 2.14-2.34(m, 2H), 2.56-2.77(m, 2H), 4.52-4.63(m, 3H, H4'+H5'), 6.36(dd, 1H,H1'), 7.32-7.58(complex pattern, 9H, 3Ph), 7.83-7.89(dd, 4H, 2Ph), 7.98-8.02(dd, 2H, 1Ph), 8.33(s, 1H), 8.62(s, 1H). ^{13}CNMR(CDCl$_3$, 75 MHz, pulse delay 3s)δ: 26.13, 32.37, 65.61, 79.56, 86.18, 128.05, 128.51, 128.71, 129.44, 129.66, 132.96, 133.30, 134.03, 143.29, 151.73, 152.03, 152.29, 166.33, 172.28.

Example 13

5'-O-Benzoyl-2',3'-dideoxy-adenosine (Alternative A)

2',3'-Dideoxy-N^6,N^6,5'-O-tribenzoyl-adenosine (0.0294 g, 5.369x10^{-5} mole) and p-methylphenol (0.0290 g, 2.685x10^{-4} mole) were dissolved in toluene (1.0 ml distiled from sodium and benzophenone) and stirred at 50 °C for 1 hour. The temperature was then raised to 110°C and kept there for 24 hours. (The conversion from 2',3'-dideoxy-N^6,N^6,5'-O-tribenzoyl-2',3'dideoxy-adenosine was fast (TLC) and the conversion from N^6,5'-O-dibenzoyl-2',3'-dideoxyadenosine to 5'-O-benzoyl-2',3' -dideoxy-adenosine was slow (TLC)). The toluene was evaporated and the residue chromatographed on a silica column with chloroform, chloroform:ethanol 99:1 and chloroform: ethanol 9:1.

Yield 0.0079 g (43.3 %). Oil, which form foams upon vacuum drying. ^{1}HNMR(CDCl$_3$, 300 MHz) δ: 2.14-2.32(m, 2H), 2.52-2.64(m, 1H), 2.65-2.77(m, 1H), 4.50-4.66(m, 3H, H4' and H5'), 5.66(broad s, 1H, NH), 6.31(dd, 1H, H1'), 7.40-7.47(m, 2H, Ph), 7.53-7.61(m, 1H,

Ph), 7.96-8.02(m, 2H, Ph) 8.05(s, 1H), 8.34(s, 1H). ^{13}CNMR ($CDCl_3$, 75 MHz, pulse delay 3s) δ: 26.40, 32.38, 65.60, 79.29, 85.84, 120.29, 128.46, 129.55, 129.62, 133.26, 138.80, 149.28, 152.95, 155.34, 166.35.

5'-O-Benzoyl-2',3'-dideoxy-adenosine (Alternative B)

N^6, 5'-O-Dibenzoyl-2',3'-dideoxy-adenosine (0.0200 g, 4.510×10^{-5} mole) and p-methylphenol (0.0122 g, 1.127×10^{-4} mole) were dissolved in toluene (1.0 ml distilled from sodium and benzophenone) and stirred at 50 °C for 1 hour. The temperature was then raised to 110°C and kept there for 24 hours. The toluene was evaporated and the residue chromatographed on a silica column with chloroform, chloroform:ethanol 99:1 and chloroform: ethanol 9:1

Yield 0.0064 g (41.8%). (^{1}HNMR- and ^{13}CNMR spectral data were identical with those obtained from the reaction of 2',3'-dideoxy-N^6,N^6,5'-O-tribenzoyl-adenosine with p-methylphenol).

Example 14

2',3'-Dideoxy-N^4-palmitoyl-cytidine and 2',3'-dideoxy-N^4,5'-O-dipalmitoyl-cytidine.

2',3'-Dideoxycytidine (0.005 g, 2.356×10^{-5} mole) was dissolved in a mixture of pyridine (0.22 ml) and dimethylformamide (0.22 ml) and cooled to 0°C. Palmitoyl chloride (8 1, 2.59×10^{-5} mole) was added with a syringe. Precipitates were formed immediately. To increase the solubility more pyridine (0.22 ml) was added. After 48 hours of stirring the

temperature was increased to 15°C. After 24 more hours at this temperature palmitoyl chloride (10 μl, 3.24×10^{-5} mole) and N,N-dimethylaminopyridine (cat. amt.) were added. The reaction mixture was stirred for 4 days at 0°C. Water (2 ml) was added and the solution was evaporated under high vacuum. Water was added four more times (4x2 ml) with complete evaporation after each addition. The products were isolated by flash chromatography on silica gel eluted with chloroform and subsequently with chloroform:ethanol 9:1.

2',3'-Dideoxy-$\underline{N}^4$-palmitoyl-cytidine

Yield: 0.0032 g (30 %) white powder. ^{1}HNMR($CDCl_3$ 200 MHz)δ: 0.87(t, 6H, 2xCH_3), 1.21-1.40(broad, 24H), 1.44-1.80(broad, 4H), 1.80-2.00(m, 2H), 2.10-2.25(m, 1H), 2.30-2.42(t, 4H), 2.43-2.60(m, 1H), 3.81 and 4.07(dxAB, 2H H5') 4.20-4.27(m, 1H, H4'), 6.07(dd, H1'), 7.40(H5), 8.15-8.25(broad, 1H,NH). 8.37(d, H6, $\underline{J}$ 7.32 Hz).

2',3'-Dideoxy-$\underline{N}^4$,5'-$\underline{O}$-dipalmitoyl-cytidine

Yield: 0.0049 g (30 %) white powder

Example 15

2',3'-Dideoxy-$\underline{N}^4$-hexanoyl-cytidine and 2',3'-dideoxy-$\underline{N}^4$,5'-$\underline{O}$-dihexanoyl-cytidine

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2',3'-Dideoxycytidine (0.0050 g, 2.356×10^{-5} mole) was dissolved in a mixture of pyridine (0.22 ml) and dimethylformamide (0.22 ml) and cooled to 0°C. Hexanoyl chloride (3.7 μl, 2.60×10^{-5} mole) was added with a syringe. The resulting mixture was stirred at 0°C for 48 hours.

The temperature was increased to 15°C and the mixture stirred for 24 more hours when hexanoyl chloride (3.7 μl) and N,N-dimethylaminopyridine (cat. amt.) were added. The resulting solution was stirred at 0°C for 5 days. The solvents were then evaporated at high vacuum. Water was added four times (4x2 ml) with complete evaporation after each addition. The products were isolated by chromatography on a silica column eluted with chloroform and chloroform: ethanol 9:1.

2',3'-Dideoxy-N^4-hexanoyl-cytidine

Yield: 0.0018 g (24 %) white powder. ^{1}H NMR($CDCl_3$, 200 MHz)δ: 0.88(t 3H), 1.15-1.40(m, 4H), 1.55-1.75(m, 2H), 1.85-1.98(m, 2H), 2.10-2.25(m, 2H), 2.41(t, 2H), 2.4-2.6(m, 2H), 3.93(dxAB, J AH4' 2.62 Hz, J BH4' 3.92 Hz, JAB 12.00 Hz, 2H), 4.25(m, 1H, H4'), 6.06(dd, 1H, H1'), 7.41(broad d, 1H, H5'), MSCI(isobutane): 310(M+1, 2.6), 252(3.3), 250(4.0), 248(2.5), 212(4.8), 211(12.5), 210(100.0), 201(3.1), 199(4.3), 154(2.7), 153(9.8), 152(5.5), 138(2.9), 116(2.4), 113(3.6), 112(24.6), 109(2.6), 101(35.9), 85(4.3), 83(9.0).

2',3'-Dideoxy-N^4-5'-O-dihexanoyl-cytidine

Yield: 0.0031 g (32 %) white powder. ^{1}H NMR($CDCl_3$, 200 MHz)δ: 0.89(broad t, 6H, 2-CH_3), 1.2-1.4(m, 10H), 1.5-1.85(m, 5H), 1.85-2.10(m, 1H), 2.10-2.25(m, 1H), 2.30-2.50(t, 4H, 2xCH_2-CO), 2.45-2.65(m, 1H), 4.25-4.50(m, 3H, H4'+H5'), 6.05(d, H1'), 8.18(d, 1H, H6), 8.0-8.5(broad, 1H, NH). MSCI(isobutane): 408(M+1, 3.5), 311(1.0), 310(2.3), 247(1.0), 245(2.9), 233(1.2), 211(3.7), 210(11.1), 200(12.0), 199(100), 148(2.5), 147(22.4), 117(3.2), 112(7.6), 99(9.5), 83(17.9), 88(17.0), 81(6).

Example 16

N^4-Benzyloxycarbonyl-2',3'-dideoxy-5'-O-ethyloxycarbonyl-cytidine.

N^4-Benzyloxycarbonyl-2',3'-dideoxycytidine (0.0358 g, 1.037×10^{-4} mole) was dissolved in tetrahydrofuran (1.0 ml, distilled from sodium and benzophenone) and cooled to -78°C. Sodium hydride (0.0045 g 80 % in oil, 1.05×10^{-4} mole) was added, and the mixture was allowed to reach room temperature. The reaction mixture was recooled to 0°C when the hydrogen gas evolution ceased. Ethyl chloroformate (0.0111 ml, 1.1403×10^{-4} mole (98%)) was added and the reaction was stirred at room temperature for 6 hours. Ethyl chloroformate (0.0111 ml, 1.1403×10^{-4} mole) was added once more and the stirring continued for 4 more hours. Saturated ammonium chloride (1ml) was added and the whole mixture evaporated at high vacuum. The resulting solid (including NH_4Cl) was loaded on a silica column and the product eluted with chloroform:ethanol 99:1 and chloroform:ethanol 9:1.

Yield: 0.0350 g (80.9 %). Oil. ^{1}HNMR($CDCl_3$ 300 MHz) δ : 1.34(t, CH_3), 1.70-1.86(m, 1H), 1.97-2.10(m, 1H), 2.10-2.23(m, 1H), 2.48-2.62(m, 1H), 4.24(k, $\underline{CH_2}$-CH_2), 4.30-4.50(m,3H, H4'+H5'), 5.22(s, $\underline{CH_2}$-O). ^{13}C NMR($CDCl_3$, 75 MHz) δ : 14.23, 24.81, 33.20, 64.50, 67.36, 67.87, 79.55, 88.06, 94.13, 134.95, 144.05, 152.21, 154,94, 162.09.

Example 17

2',3'-Dideoxy-5'-O-ethyloxycarbonyl-cytidine

N^4-Benzyloxycarbonyl-5'-O-ethyloxycarbonyl-2',3'-dideoxy-cytidine (0.0350 g, 8.387×10^{-5} mole) was added to a suspension of palladium on charcoal (5% Pd, 0.0040 g) in ethanol (1.0 ml). The air was replaced with nitrogen by repeated suction and addition of nitrogen. Hydrogen gas was added to the evacuated flask (15 ml flask) with a gastight syringe (5 ml). The reaction flask was shaken with this hydrogen pressure (1/3 atm) for 1 hour. Thin layer chromatography revealed partial consumption of the substrate and formation of a more polar product. The reaction slowed down after a while and the hydrogen pressure was increased to 1 atm. After a further 30 minutes more palladium on charcoal was added (0.0200 g) and the reduction continued until almost all the substrate was consumed (TLC) (2 hours).

The solvent was evaporated and the resulting black (charcoal) solid was subjected to a combined filtration and chromatography on a silica column. The eluents were chloroform, chloroform:ethanol 99:1 and chloroform:ethanol 9:1.

Yield: 0.0080 g (38.9 %) glassy material. ^{1}HNMR($CDCl_3$ 300 MHz)δ: 1.33(t, CH_3), 1.65-1.85(m, 1H), 1.90-2.18(m, 1H), 2.40-2.55(m, 1H), 4.23(k, $\underline{CH_2}$-CH_3), 4.28-4.43(m, 3H, H4'+H5'), 5.74(d, H5, J 7.44 Hz), 6.07(dd, 1H, H1'), 7.78(d, 1H, H6, J 7.44 Hz), 5.2-7.3(very broad, 2H, NH_2). ^{13}C NMR($CDCl_3$, 75 MHz, pulse delay 3s)δ: 14.24, 25.31, 32.99, 64.39, 67.90, 78.68, 87.36, 93.54, 140.90, 154.99, 155.87, 165.63.

Example 18

5'-O-Butyroyl-2',3'-dideoxy-cytidine and N[4],5'-O-dibutyroyl-2',3'-dideoxy-cytidine.

2',3'-Dideoxy-cytidine (0.0200 g, 9.467×10^{-5} mole) and N,N-dimethylaminopyridine (0.0116 g, 9.467×10^{-5} mole) were dissolved in a mixture of pyridine (1 ml) and dichloromethane (1 ml). The resulting mixture was cooled to 0°C and n-butyric anhydride (0.0236 g, 1.420×10^{-4} mole) (95%) was added with a syringe. The mixture was stirred at room temperature for 16 hours, water (2 ml) was added. Water and organic solvents were removed by high vacuum evaporation. The products were purified by chromatography on a silica column with chloroform:ethanol 9:1 as eluent.

5'-O-butyroyl-2',3'-dideoxy-cytidine

Yield: 0.0168 g (47.0 %). ^{1}HNMR($CDCl_3$, 100 MHz) δ: 0.96(t, CH_3), 1.47-1.83(m, 1H), 1.68(k, CH_2), 1.83-2.20(m, 2H), 2.20-2.67(m, 1H), 2.35(t, CH_2), 4.35(broad, 3H, H4'+H5'), 5.76(d, 1H, H5, *J* 7.3 Hz), 6.04(dd, 1H, H1'), 5.5-7.2(very broad, 2H, NH_2), 7.73(d, 1H, H6).

N[4],5'-O-dibutyroyl-2',3'-dideoxy-cytidine

Yield: 0.0021 g (4.1 %). Oil. ^{1}HNMR($CDCl_3$ 100 MHz) δ: 0.98(t, CH_3), 1.00(t, CH_3), 1.7(2xk, 2-CH_2), 2.0-2.5(2xt, 2-CH_2), 4.37(broad, 3H, H4'+H5'), 6.05(dd, 1H, H1'), 7.42(d, 1H, H5, *J* 7.8 Hz), 8.18(d, 1H, H6, *J* 7.8 Hz), 8.0(broad, 1H, NH), H2' and H3' obscured by other peaks,

Example 19

2',3'-Dideoxy-5'-O-propioyl-cytidine and 2',3'-Dideoxy-N^4,5'-O-dipropioyl-cytidine

---

2',3'-Dideoxy-cytidine (0.0200 g, 9.467×10^{-5} mole) and N,N-dimethylaminopyridine (0.0116 g, 9.467×10^{-5} mole) were dissolved in a mixture of pyridine (1 ml) and dichloromethane (1 ml). The resulting mixture was cooled to 0°C and propionic anhydride (0.0185 g, 1.42×10^{-4} mole) was added with a syringe. The mixture was stirred at room temperature for 14 hours, water (2 ml) was added. Water and organic solvents were removed by high vacuum evaporation. The products were purified by chromatography on a silica column with chloroform:ethanol 9:1 as eluent.

2',3'-Dideoxy-N^4-5'-O-dipropioyl-cytidine

Yield: 0.0132 g (43.1 %). Oil. ^{1}HNMR($CDCl_3$, 100MHz) δ : 1.19(t, $2CH_3$), 1.43-2.78(several multiplets, 4H, H2'+H3'), 2.46(2xk, $2CH_2$), 4.38(broad, 3H, H4'+H5'), 6.60(dd, 1H, H1'), 7.44(d, 1H, H5, J 7.3 Hz), 6.19(d, 1H, H6, J 7.3 Hz), 9.0(broad, 1H, NH).

2',3'-Dideoxy-5'-O-propioyl-cytidine

Yield: 0.0085 g (33.5 %). Oil. ^{1}HNMR($CDCl_3$, 100 MHz). δ : 1.18(t, CH_3), 1.43-2.70(several multiplets 4H, H2'+H3'), 2.40(k, CH_2), 4.33(broad, 3H, H4'+H5'), 5.73(d, 1H, H5, J 7.8 Hz), 6.50(dd, 1H, H1'), 7.79(d, 1H, H6, J 7.8 Hz), 5.0-7.3(very broad, 2H, NH_2).

Pharmaceutical Example A

Preparation of capsules for oral use

5'-*O*-Butyryl-2',3'-dideoxy-adenosine	50 mg
Amylum maydis	q.s.

The powder is mixed and filled into hard gelatin capsules (Capsugel Size 00).

Pharamceutical Example B

Preparation of an ointment

N^6,5'-*O*-Dibenzoyl-2',3'-dideoxy-adenosine	1 g
Liquid paraffin	100 g
White soft paraffin	to 1000 g

White soft paraffin was melted and incorporated into the liquid paraffin and stirred until the mixture was cold. *N*^{6},5'-*O*-di-benzoyl-2',3'-dideoxy-adenosine was triturated with a portion of the basis and gradually the remainder of the basis was incorporated. The ointment was filled into lacquered aluminium tubes (20 g) and sealed. The ointment contained 0.1 % *N*^{6},5'-*O*-dibenzoyl-2',3'-dideoxy-adenosine.

Pharmaceutical Example C

Suspension for parenteral administration

2',3'-Dideoxy-5'-*O*-palmitoyl-cytidine	200 gram
Polysorbate 80	3 gram
Sorbitol	400 gram
Benzyl alcohol	8 gram
Water	ad 1000 ml
1M HCl	q.s.

Polysorbate 80, Sorbitol and benzyl alcohol were dissolved in 500 ml distilled water. 2',3'-Dideoxy-

5'-O-palmitoyl-cytidine was screened through a 0.15 mm sieve and dispersed in the solution under vigorous stirring. The pH was adjusted to 4.5 by dropwise addition of 1M HCl. Water was added to 1000 ml, the suspension was filled in 1 ml vials The vials were sterilized by -radiation. Each vial contained 200 mg 2',3'-dideoxy-5-O-palmitoyl-cytidine.

Pharmaceutical Example D

Preparation of tablets

	Gram
$\underline{N}^4$,5'-O-diacetyl-2',3'-dideoxy-cytidine	200
Lactose	85
Polyvinylpyrrolidone	5
Starch	42
Talcum powder	15
Magnesium stearate	3

$\underline{N}^4$,5'-O-Diacetyl-2',3'-dideoxy-cytidine and lactose were screened through a 0.15 mm sieve and mixed together for 10 minutes. The mixed powder was wetted with an aqueous solution of polyvinyl-pyrrolidone. The mass was granulated, and the dried (40 °C) granulate was mixed with starch, talcum powder and magnesium stearate. The granulate was compressed into tablets. The tablet diameter was 11 mm, the tablet was 350 mg and each tablet contained 200 mg $\underline{N}^4$,5'-O-diacetyl-2',3'-dideoxy-cytidine.

Pharmaceutical Example E

Preparation of a suspension for rectal administration

Methyl parahydroxybenzoate (70 mg) and propyl parahydroxy-benzoate (15 mg) were dissolved in water (100 ml) at 90 °C. After cooling to 30 °C methyl cellulose (2g) was added and the mixture was agitated for 3 hours. 1 gram $\underline{N}^4$-benzoyl-2',3'-dideoxy-cytidine

was screened through a 0.15 mm sieve, and dispersed in the solution under vigorous stirring. The suspension was filled in a 100 ml tube. The suspension contained 10 mg $\underline{N}^4$-benzoyl-2',3'-dideoxy-cytidine/ml.

Pharmaceutical Example F

Preparation of oral suspension

	Gram
2',3'-dideoxy-$\underline{N}^4$-hexanoyl-cytidine	10
Carboxymethyl cellulose	1.5
Sorbitol	200
Sodium benzoate	1.0
Orange essence	0.3
Apricot essence	0.7
Ethanol	50
Water	236.5

Carboxymethyl cellulose, sorbitol and sodium benzoate were dissolved in water with stirring for 2 hours. A solution of the essences in ethanol was added. 2',3'-Dideoxy-$\underline{N}^4$-hexanoyl-cytidine was screened through a 0.15 mm sieve and dispersed in the solution under vigorous stirring. The suspension (10 gram) was filled in a 20 ml tube. Each tube contained 200 mg 2',3'-dideoxy-$\underline{N}^4$-hexanoyl-cytidine.

Pharmaceutical Example G

Preparation of injection solution

10 mg 5'-$\underline{O}$-acetyl-2',3'-dideoxy-cytidine were dissolved in 10 ml 0.9 % sodium chloride. pH was adjusted to 4.5 with 1N HCl. The solution was sterile filtered and filled into a 10 ml vial. The solution contained 1 mg 5'-$\underline{O}$-acetyl-2',3'-dideoxy-cytidime/ml.

Pharmaceutical Example H

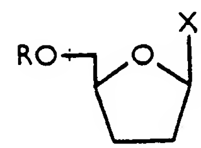
Preparation of tablets (controlled release formulation)

	Gram
2',3'-Dideoxy-5'-O-ethyloxycarbonyl-cytidine	500
Hydroxypropylmethylcellulose (Methocel K15)	120
Lactose	45
Povidone	30
Magnesium stearate	5

2',3'-Dideoxy-5'-O-ethyloxycarbonyl-cytidine, hydroxypropyl methylcellulose and lactose were mixed together for 20 minutes and granulated with a solution of povidone. Magnesium stearate was added and the mixture was compressed into tablets. The tablet diameter was 13 mm, the tablet weight was 700 mg and each tablet contained 500 mg 2',3'-dideoxy-5'-O-ethyloxycarbonyl-cytidine.

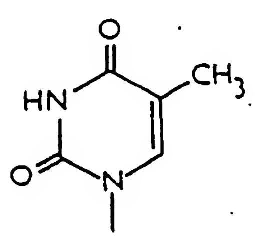
CLAIMS:

1. A pharmaceutical composition comprising as active ingredient one or more compounds of formula (I)



(I)

wherein R is a hydrogen atom or a physiologically acceptable acyl group of formula R^1.CO- or R^1.O.CO-, R^1 being an optionally substituted alkyl or aryl group, and X is selected from



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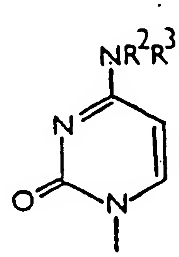

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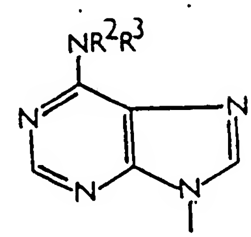

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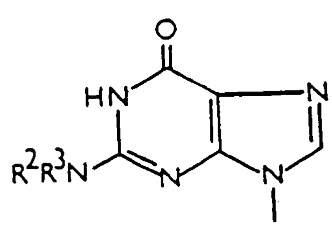
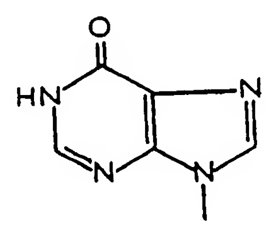


and



;

wherein R^2 and R^3, which may be the same or different, are each a hydrogen atom or a physiologically acceptable acyl group of formula R^4.CO- or R^4.O.CO-, R^4 being an optionally substituted alkyl or aryl group, with the proviso that at least one of R and R^2 must be an acyl group, and/or salts thereof.

2. A pharmaceutical composition as claimed in claim 1 wherein R^2 and R^3 are hydrogen atoms and R is a group R^1.O.CO-, R^1 being an optionally substituted alkyl or aryl group.

3. A pharmaceutical composition as claimed in claim 1 wherein R^2 is a group of formula R^4.CO or R^4.O.CO-, R^4 being an optionally substituted alkyl or aryl group, R^3 is a hydrogen atom or a group as defined for R^2 and R is a hydrogen atom or a group of formula R^1. CO- or R^1.O.CO-, R^1 being an optionally substituted alkyl or aryl group.

4. A pharmaceutical composition as claimed in any preceding claim wherein R, R^2 and R^3 are independently selected from hydrogen atoms and C_{1-20} acyl groups.

5. A pharmaceutical composition as claimed in any preceding claim wherein X is a substituted or unsubstituted thymine radical.

6. A pharmaceutical composition as claimed in any preceding claim further comprising an antiviral agent selected from acyclovir, phosphonoformate, suramin, Evans Blue, interferons and azidothymidine.

7. A pharmaceutical composition as claimed in any preceding claim for use in combating neurological disorders caused by neurotropic viruses.

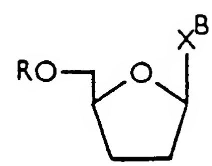
8. Compounds of formula (I) wherein R and X are as defined in claim 1 with the further proviso that when R is an acetyl group then X is not a thymine radical; when R is a benzoyl group then X is not a thymine radical or an N-unsubstituted cytosine radical and when R is a 3-(trifluoromethyl)-benzoyl group then X is not an N-unsubstituted adenine radical; and salts thereof.

9. Compounds as claimed in claim 8 wherein R^2 and R^3 are hydrogen atoms and R is a group $R^1.O.CO-$, R^1 being an optionally substituted alkyl or aryl group.

10. Compounds as claimed in claim 8 wherein R^2 is a group of formula $R^3.CO-$ or $R^3.O.CO-$, R^3 being an optionally substituted alkyl or aryl group, R^2 is a hydrogen atom or a group as defined for R^2 and R is a hydrogen atom or a group of formula $R^1.CO-$ or $R^1.O.CO-$, R^1 being an optionally substituted alkyl or aryl group.

11. Compounds of formula (I) as defined in claim 1 and/or salts thereof for use in combating neurological disorders caused by neurotropic viruses.

12. A process for the preparation of a compound of formula (I) as defined in claim 7 or a salt thereof which comprises reaction of a compound of formula (II)



(II)

[wherein R is as defined in claim 8 and X^B is as defined in claim 8 for X except that R and R^2 and/or R^3 may each additionally represent a protecting group, with the proviso that at least one of R, R^2 and R^3 is a hydrogen atom] with an acylating agent serving to introduce an acyl group R^1CO-, R^1OCO-, R^4CO- or R^4OCO-, followed where required by removal of any protecting groups and/or unwanted acyl substituents.

13. A method of treatment of viral disorders wherein an effective dose of a compound of formula (I) as defined in claim 1 and/or a salt thereof is administered to a patient suffering from such a disorder.

14. A method as claimed in claim 11 in which the said disorder is caused by a neurotropic virus.

15. A method as claimed in claim 1 in which the virus is an HIV virus.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 88/00224

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 405/04; C 07 D 473/34

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 473/00; C 07 D 405/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4177348 (UNITED STATES GOVERNMENT) 4 December 1979, see columns 1,2: summary; columns 15,16: claims --	1-11
A	EP, A, 0206497 (THE WELLCOME FOUNDATION) 30 December 1986, see page 8, formula II; page 9, last two lines; page 10, lines 1-4 cited in the application ------	1

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16th June 1988	11 JUIL. 1988
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8800224 SA 21362

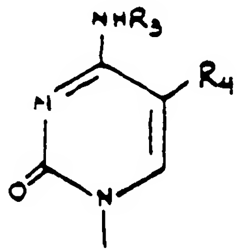
This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 28/06/88
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4177348	04-12-79	US-A- 4232154	04-11-80
EP-A- 0206497	30-12-86	JP-A- 61280500 AU-A- 5744086	11-12-86 20-11-86

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

wherein:
R_1 is selected from the group of hydrogen, trifluoromethyl or saturated or unsaturated C_{1-5} alkyl groups;
R_4 and R_5 are independently selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-5} alkyl, bromine, chlorine, fluorine, or iodine;
R_5 is selected from the group of hydrogen, cyano, carboxy, ethoxycarbonyl, carbamoyl, or thiocarbamoyl; and
X and Y are independently selected from the group of hydrogen, bromine, chlorine, fluorine, iodine, amino or hydroxyl groups.

5. A process according to any of claims 1 to 3 wherein R_2 is:



wherein R_3 is selected from the group of hydrogen, trifluoromethyl or saturated or unsaturated C_{1-5} alkyl groups and R_4 is selected from the group of hydrogen, hydroxymethyl, trifluoromethyl, substituted or unsubstituted, saturated or unsaturated C_{1-5} alkyl, bromine, chlorine, fluorine, or iodine.

6. A process according to any one of claims 1 to 5 wherein the compound of formula (I) is selected from:
Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-hydroxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-benzoyloxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(N_4'-acetyl-cytosin-1'-yl)-1,3-oxathiolane, and mixtures thereof; and
Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-3-oxo-1,3-oxathiolane;
Cis-2-hydroxymethyl-5-(N-dimethylamino-methylene cytosin-1'-yl)-1,3-oxathiolane;
Bis-Cis-2-succinyloxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane; trans-2-benzoyloxymethyl-5-(6'-chloropurin-N-9'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(6'-hydroxypurin-N-9'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(uracil-N-1'-yl)-1,3-oxathiolane;
Cis-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, trans-2-benzoyloxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane, and mixtures thereof;
Cis-2-hydroxymethyl-5-(thymin-N-1'-yl)-1,3-oxathiolane;
and pharmaceutically acceptable derivatives thereof in the form of a racemic mixture or single enantiomer.

7. A process according to any one of claims 1 to 5 wherein the compound of formula (I) is Cis-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane, and pharmaceutically acceptable derivatives thereof.

8. A process according to any one of claims 1 to 7 wherein the compound of formula (I) is obtained in the form of a racemic mixture.

9. A process according to any one of claims 1 to 7 wherein the compound of formula (I) is obtained substantially in the form of a single enantiomer.

10. A process according to any one of claims 1 to 9 wherein in step (a) the group L is selected from a group consisting of alkoxy carbonyl, iodine, bromine, chlorine or -OR, where R is a substituted or unsubstituted, saturated or unsaturated alkyl group or R is a substituted or unsubstituted aliphatic or aromatic acyl group.

11. A process according to any one of claims 1 to 10 wherein step (a) the compound of formula (VIII) is reacted with a silylated purine or pyrimidine base in a compatible solvent in the presence of a Lewis acid or

12. A method for the preparation of a pharmaceutical formulation comprising admixing a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable derivative thereof with a pharmaceutically acceptable carrier therefor.